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Errors Involving Pediatric Patients Receiving Chemotherapy: A Literature Review

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A review of mishaps involving pediatric patients receiving anticancer chemotherapy was undertaken in order to assist intervention. Although the case literature is too sparse to provide definite recommendations, suggestions for management are made in the event of an error with a high risk (based on the case literature) of life-threatening toxicities. It is recommended that all incidents be reported in the literature in order to provide a basis for devising standard treatment protocols. It is also suggested that studies using animal models continue to be done in order to provide more experimental data about toxicities and potentially beneficial rescue therapies. © 1996 Wiley-Liss, Inc.

Key words: antineoplastic agents, medication errors, children

INTRODUCTION

A child in our institution received an intrathecal overdose of cytarabine. Although one report of a similar case had been published [1], no information could be found about a protocol for management. A review of the literature was undertaken to determine if there was enough information to develop protocols for our institution, involving any antineoplastic agent, should such a mishap recur. The results of this review are presented for the types of incidents that have been associated with severe toxicities or a fatal outcome.

METHODS

Literature Search

The MEDLINE database was searched over the years 1966 through 1993 for pertinent articles. An article was considered evaluable if an error (wrong dose and/or wrong route) occurred during anticancer chemotherapy or if an antineoplastic agent was taken by or given to a person not meant to receive it (if the dose and/or route were inappropriate). Articles were included for review if the age of the person reported on was less than 25 years, on the assumption that an incident involving a young adult would be comparable with one involving an adolescent.

Articles with information about adult patients were also examined (1) if a case report described a beneficial intervention not found in the literature reporting experiences with pediatric patients, (2) if the experiences were similar enough to those involving pediatric patients to justify including the material, or (3) if there was a paucity of published pediatric cases.

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Other Oncology Treatment Centers and Manufacturers

Other Canadian oncology centers were contacted to learn if they knew of protocols for the management of medication errors involving antineoplastic agents. The drug information services of nine manufacturers were requested to forward any unpublished information that they might have.

RESULTS

Literature Search

The MEDLINE search initially yielded approximately 5,000 references. After screening titles and abstracts, and then reviewing articles of potential interest, 40 articles were found that met the inclusion criteria. Table I lists the results of the literature search.

Other Centers and Manufacturers

No Canadian center had existing protocols for the management of antineoplastic medication errors or knew of such a resource. One manufacturer forwarded a copy of a published case report. No manufacturer provided information on unpublished cases.

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TABLE I. Results of MEDLINE Search for Articles Describing Incidents Involving Pediatric Patients Receiving Antineoplastic Agents

Drug	Error	Cases	Fatalities	Ref.
Methotrexate	IT[a] overdose	9	2	2–6
	Oral poisoning	2	0	7
Dactinomycin	IV overdose	1	0	8
Chlorambucil	Oral overdose	1	0	9
	Oral poisoning	4	0	10–13
Melphalan	IV overdose	1	0	14
Cisplatin	IV overdose	1	0	15
Mitoxantrone	IV overdose	1	0	16
Doxorubicin	IT injection	1	0	17
Daunorubicin	IT injection	1	1	18
Cytarabine	IT overdose	1	0	1
5-Azacytidine	IV overdose	1	0	19
Vincristine	IV overdose	18	4	8, 20–30
	IT injection	7	7	31–37
Vinblastine	IV overdose	2	0	38, 39
6-MP[b]	Oral poisoning	1	0	40

[a]Intrathecal.
[b]6-Mercaptopurine.

Case Characteristics, Reported Toxicities, and Reported Therapies

Only those incidents that have been associated with serious toxicities or death will be reviewed in detail: methotrexate intrathecal overdose, vinca alkaloid intravenous overdose, vinca alkaloid intrathecal injection, and anthracycline intrathecal injection.

Methotrexate intrathecal overdose. Nine cases of intrathecal overdoses of methotrexate have been reported [2–6]. There were two fatalities [2,6]. In six of the nonfatal cases, the dosage range was 50–120 mg (less than a 15-fold overdose), and the age range was 2–12 years. There were no reported toxicities in four cases [3,5,6]. Two other children complained of headaches [4,6]. Although one of those two children also suffered "acute nephropathy" [6], it was not clear if this could be attributed to the overdose. Information about the seventh case was available only as a personal communication [6]: A 9-year-old child received 650 mg of methotrexate and was reported to have suffered "massive" neurological damage.

One fatal case involved a 9-year-old male who received 650 mg of methotrexate [2], a 54-fold overdose. That child began suffering seizures in less than an hour and became comatose 2 hours after the overdose. He also exhibited posturing, developed flaccid paralysis; and required mechanical ventilation. He died 1 month later of sepsis, without regaining consciousness. The second fatal case was reported as a personal communication [6]. A 7-year-old child received 1,000 mg of methotrexate, suffered "widespread" brain damage, and died a few days after the incident.

Drug removal was attempted in eight cases, beginning 45 minutes to 10 hours after injection. Cerebrospinal fluid (CSF) exchange was used in three cases (nonfatal) [3,6], and CSF removal alone was used in four (one fatal) [5,6]. The remaining case (fatal) [2] was managed first with CSF removal alone, then by CSF exchange. The case in which drug removal was not attempted was nonfatal [4]: A 24-month-old female received 85 mg of methotrexate (instead of 6 mg). She complained of mild headaches for 4 days. The amount of drug recovered was reported for one fatal case (dose 650 mg) [2]: 46.5% was recovered 1 hour after the incident, and an additional 31% was recovered 90 minutes after that.

Folinic acid was given as rescue therapy in all cases, either intravenously (IV) or intramuscularly. Stat dosages ranged from 0.9 to 8.5 mg/kg [2–5]. Maintenance dosages ranged from 0.2 to 0.6 mg/kg [2–6]. Dosages were reported for one fatal case [2]. That child received 1 mg/kg IV stat (two doses), followed by 0.2 mg/kg IV q6h for 2 weeks. There were no reports of bone marrow suppression or mucositis.

Dexamethasone, or an unidentified corticosteroid, was given as rescue therapy in six cases, either orally or IV [3,4,6]. Dosages ranged from 0.1 to 0.7 mg/kg, and durations of therapy ranged from 24 to 72 hours. Dexamethasone was also used to treat presumed cerebral edema in one fatal case [2] but did not appear to have been started immediately. Other than the two children who complained of headaches (both of whom received dexamethasone), none of the children who received overdoses under 15-fold presented with any signs or symptoms of central nervous system (CNS) toxicity, including two who did not receive a corticosteroid [5,6].

Vinca alkaloid intravenous overdose. There have been 20 published cases of a vinca alkaloid IV overdose, 18 involving vincristine [8,20–30] and 2 involving vin-

blastine [38,39]. There were four fatalities, all involving vincristine [20,22]. The average age was 10 years (± 6; mean ± SD). The mean dosage for nonfatal cases involving vincristine was 0.3 mg/kg (±0.2), while the range for fatal cases was 0.2–0.6 mg/kg. The dosages in the cases involving vinblastine were 1.5 mg/kg and 2.3 mg/kg.

Major complications included paralytic ileus, neurotoxicities, pancytopenia, and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The major risk factors for a fatal outcome were infection associated with neutropenia and hemorrhage associated with thrombocytopenia. Death occurred from 1.5–24 days after an overdose.

Gastrointestinal toxicities were common. Nausea and vomiting, diarrhea, and abdominal pain generally appeared within 48 hours. Paralytic ileus was reported in 12 cases, with a mean onset of 5 days. Six children suffered parasthesia, and 11 suffered a loss of deep tendon reflexes, as early as 24 hours after an overdose.

Central nervous system toxicity appeared, in some cases within 48 hours. Agitation and irritability were reported in several cases, sometimes lasting more than 2 months. Three children became comatose, one within an hour after an overdose. Nine children (two fatal cases) suffered seizures, beginning as early as 48 hours after an overdose, and some children continued to suffer seizures for more than 2 months.

Thrombocytopenia occurred in 14 cases. The onset was at 1–9 days, and the nadir counts ranged from 8.0 to 70.0×10^9/L. Leukocytopenia developed in 18 cases. The onset was at 3–9 days, and the mean nadir count was 1.1×10^9/L (±1.0). Frank hemorrhage occurred in 2 cases (one fatal), and fever and neutropenia in 13 (three fatal).

Double-volume exchange transfusions and plasmapheresis were used to attempt drug removal. Kosmidis et al [20] described the cases of three children with acute lymphoblastic leukemia (ALL) who received 7.5 mg/m^2 of vincristine. Each underwent a double-volume exchange transfusion 6 hours after an overdose. In two cases there was a direct relationship between the percentages of dose recovered (72% and 58%, respectively) and the durations of toxicities: marrow aplasia (4 and 9 days), peripheral neuropathy (15 and 42 days), paralytic ileus (3 and 5 days), and hypertension (5 and 14 days). In the third case, only 7% of the dose was recovered. Fever, neutropenia, and bloody diarrhea persisted, despite antibiotic therapy and platelet transfusions. The child died on day 9, when he suffered a cardiac arrest and could not be resuscitated.

Winter and Arbus [39] reported the case of a 3-year-old boy with histiocytosis X who received 30 mg of vinblastine. That child underwent a double-volume exchange transfusion beginning 4 hours later. The amount of drug recovered was not given. He became febrile and suffered pancytopenia, paralytic ileus, SIADH, and hypertension. He was reported to have been healthy 9 months later.

In contrast, Pierga et al. [27] described the case of an 18-year-old male who received two 8-mg doses of vincristine 12 hours apart. Plasmapheresis, of 1.5 times the estimated plasma volume, was carried out beginning 6 hours after the second dose. Assuming a plasma volume of 3.5 L, less than 1% of the 16 mg was recovered. The patient suffered neutropenia, loss of deep tendon reflexes, an abnormal electroencephalogram (EEG), and SIADH.

Folinic acid was used as rescue therapy in 10 cases (20–24,28,29,38] and was reported to have reduced the duration of neurotoxicities, or toxicity to bone marrow, in 6 [20,21,23,24,29]. The dosage, except for one of those six cases, was greater than 2 mg/kg/day.

Eight children developed SIADH. The mean time to onset was 6 days, and the mean duration was 8 days. Fluid restriction (regimens not described) was reported to have been effective in three cases [22,27,28] and ineffective in three [20,22,24].

Vinca alkaloid intrathecal injection. Seven cases of the intrathecal injection of vincristine have been published [31–37]. The ages ranged from 15 months to 23 years. The times to discovery of the error ranged from immediately to 3 hours. The dosages ranged from 0.7 to 3.0 mg. All cases were fatalities, and the times to death ranged from 3 to 36 days. (In one exceptional circumstance, a patient was kept alive by support measures for almost a year, but diffuse encephalopathy had been demonstrated by day 11 [35].)

Histological studies of neurons exposed to vincristine revealed intracellular changes, presumably produced by the binding of vincristine to microtubulin [32,34]. The putative effects of these changes were an interruption in axoplasmic flow, loss of neuron function, and eventually cell death. Clinically, patients experienced ascending paralysis and coma.

Drug removal was attempted in four cases: CSF exchange with normal saline at 13 mL/kg stat via lumbar puncture [34]; CSF removal at 1 mL/kg via lumbar puncture, once 30 minutes after injection and once 24 hours later [37]; CSF removal at 1.7 mL/kg stat via lumbar puncture [35]; and ventriculolumbar "washout" with normal saline, to a total of 645 mL, beginning 4.5 hours after injection and continuing until 12.5 hours later (with what appeared to be a 2.5 hour interruption) [36]. The amount of drug removed was reported for one case: 23% of a 1.2 mg dose was recovered, 30 minutes after injection, by CSF removal [37].

Corticosteroids were used as rescue therapy in three cases. Two children received hydrocortisone (1.3 mg/kg

q72h and 5 mg/kg q24h) intrathecally [31,37]. A third child received IV dexamethasone (dosage not reported) [35].

Folinic acid was used as rescue therapy in four cases. Two children received 1.4 and 0.3 mg/kg IV q3h [31,32]. In a third case [36], a 23-month-old female was given folinic acid 8 mg/kg by IV push stat, followed by 8 mg/kg/h by IV infusion (for 1 hour), and then 2 mg/kg/h. She was reported to have had a transient recovery of deep tendon reflexes.

Anthracycline intrathecal injection. There have been two published cases of the intrathecal injection of an anthracycline. A child who received 30 mg/m^2 of doxorubicin survived [17], while a second child, who received 25 mg/m^2 of daunorubicin, died [18].

In the fatal case, CSF exchange with normal saline was started 1 hour after the incident and was continued for 3 hours. Continuous gravity drainage of CSF was done for the next 36 hours. Induction therapy for ALL (vincristine, prednisone, and L-asparaginase) recommenced on day 4. Seventeen days after the incident, the patient became areflexic, with flaccid paralysis. She then became comatose and required ventilation. She died 9 weeks after the incident, without regaining consciousness, when ventilation was discontinued. At that time, an EEG revealed no electrical activity, and a radionuclide brain scan demonstrated no cerebral blood flow.

The child who survived did not undergo any attempt at drug removal. She also became comatose and developed severe tetraventricular hydrocephalus, which was discovered 16 days after the incident. The latter resolved after the installation of a ventriculoperitoneal shunt. She was reported to have had no residual neuropathy 9 months after the incident.

Corticosteroids were used in both cases. Fever, nausea, and vomiting began 12 hours after the intrathecal injection of doxorubicin. These symptoms resolved with dexamethasone and mannitol (dosages and durations of therapy not reported). Methylprednisolone 20 mg/kg IV q6h, and hydrocortisone 2 mg/kg via lumbar puncture, were used in the daunorubicin case.

Cases involving other antineoplastic agents. There were several case reports describing overdoses, or poisonings, with other agents. For most drugs, only one published report was found. A summary of this literature is presented in Table II. There were no fatalities among these cases.

TABLE II. Summary of the Dosages and Toxicities From Selected Case Reports

Dose	Toxicities
Methotrexate oral poisoning [7]	
202.5 mg (possible total) (two siblings)	• No acute toxicities
Dactinomycin + vincristine IV overdose [8]	
2.5 mg dactinomycin + 1 mg vincristine (on 2 consecutive days)	• Seizure • Edema, erythema, bullae, purpurae • Gastrointestinal ulceration
Chlorambucil oral overdoses/poisoning [9–13]	
Overdose (1 case): 1.5 mg/kg/day for 8 days	• Seizures • Pancytopenia
Poisonings (4 cases): 1.3–5 mg/kg	• Nausea and vomiting
Melphalan IV overdose [14]	
140 mg	• Pancytopenia [14]
Cisplatin IV overdose [15]	
90 mg/m^2/day for 5 days	• Pancytopenia • Hyperchloremic metabolic acidosis • Protracted vomiting and diarrhea • No evidence of ototoxicity • No elevation in serum creatinine
Mitoxantrone IV overdose [16]	
98 mg	• Myelosuppression • Reversible cardiopathy
Cytarabine intrathecal overdose [1]	
200 mg	• No acute toxicities
5-Azacytidine IV overdose [19]	
266 mg/m^2	• Nausea and vomiting • Severe myalgia • Somnolence progressing to coma
6-Mercaptopurine oral poisoning [40]	
1,500 mg	• Dizziness and headache • Right upper left quadrant pain

DISCUSSION

The case literature on pediatric patients involved in some mishap with an antineoplastic agent is too sparse to devise standard treatment protocols. Nevertheless, some general statements can be made. If a means of drug removal exists, this is likely to be the most beneficial intervention. If a specific antidote to a drug exists, for example, folinic acid in the event of a methotrexate overdose, its use would be a rational intervention.

This discussion presents suggestions for the management of incidents that, based on the case literature, have been associated with life-threatening toxicities. It begins with an examination of methods for drug removal.

Drug Removal

Drug removal appears to offer the best opportunity for a good outcome. The methods described in the case literature are invasive procedures. The risks of using them must be weighed against the evidence that severe toxicities, or death, may occur if drug removal is not successful.

Methotrexate intrathecal overdose. Reviewed cases described overdoses of less than 15-fold or greater than 50-fold (e.g., 650 mg). The former were satisfactorily managed with CSF exchange and/or removal. Pediatric cases involving overdoses greater than 50-fold, however, produced serious toxicities or death. Drug removal was

attempted in all three of those cases but did not appear to affect outcome.

In contrast, an adult patient survived (with no sequelae) a dose of 625 mg after undergoing CSF drainage and ventriculolumbar perfusion [41], by which 97% of the dose was recovered. This was accomplished by inserting a Scott ventricular cannula into the frontal horn of the right lateral ventricle. A total of 550 mL of normal saline, warmed to body temperature, was instilled into the cannula in 5 mL aliquots over 4 hours and was allowed to drain via lumbar puncture. The rate of perfusion was such that one volume of normal saline, equal to the estimated volume of CSF, was instilled per hour [42].

It may not be necessary to attempt drug removal if the overdose is less than 15-fold. One child, who received a 14-fold overdose, did not undergo drug recovery at all and had no ill effects. It is also possible that an overdose of 15-fold to 50-fold could be managed with CSF exchange alone, or even without attempting drug removal. Nevertheless, in the absence of any reported experiences, it would be prudent to consider drug removal in such a case.

In the event of a massive intrathecal overdose of methotrexate, CSF exchange or CSF removal, with normal saline, until perfusion can be started, should be seriously considered. It is suggested that the rate of perfusion be set in proportion to the estimated CSF volume.

Vinca alkaloid intravenous overdose. Double-volume exchange transfusion appears to be more rational, compared with plasmapheresis, because of the pharmacokinetic characteristics of vinca alkaloids. They avidly bind to tissue and plasma protein and are taken up by formed elements in the blood, particularly by platelets [43,44]. Therefore, more drug would be expected to be recovered by transfusion. Based on the experiences reported by Kosmidis et al., transfusion is effective for removing drug and thus reducing the duration of toxicities.

Vinca alkaloid intrathecal injection. All reported pediatric cases have been fatalities. One child did undergo *ventriculolumbar* "washout," but this attempt at drug removal started 4.5 hours after injection, was carried out for only 12.5 hours, and used normal saline as the washout fluid [36].

In comparison, ventriculolumbar perfusion was effective for the management of the only known survivor (an adult) of the intrathecal injection of vincristine [45]. CSF exchange with Ringer's lactate was started immediately. After the patient had been prepared, perfusion was started with plain Ringer's lactate running at 150 mL/h for an unspecified period of time, followed by perfusion with a protein solution at 75 mL/h, over a total of 24 hours. The protein solution was 25 mL of fresh-frozen plasma per liter of Ringer's lactate. Ninety-five percent of the 2 mg dose was removed. The patient recovered from the incident with residual, but nonprogressive, lower-limb neuropathy. He was reported to have died 3 months later from his primary disease (Burkitt's lymphoma).

Because of the affinity of vinca alkaloids for proteins, it is likely that the addition of plasma to the perfusion fluid increased the effectiveness of this intervention [43,44]. However, the case was described only in a letter, and no rationale was offered for the use of plasma rather than another source of protein (for example, albumin).

The suggested intervention in the event of the intrathecal injection of a vinca alkaloid is CSF exchange and ventriculolumbar perfusion, using a solution of Ringer's lactate and some protein source from the start. In the adult case [45], the rate of perfusion with the protein solution was such that a volume of solution equal to approximately one-half the estimated CSF volume was instilled per hour. This was done in order to maintain a concentration of protein in the CSF space of 1.5 mg/mL. In the case of a younger patient, with a smaller CSF volume, it is suggested that the rate be adjusted proportionately.

The estimated half-life of intrathecally injected vincristine is 5 days, based on CSF vincristine concentrations reported in one case [32]. While it might be appropriate to carry out ventriculolumbar perfusion for longer than 24 hours, almost the entire dose in the adult case was recovered over that length of time.

The effectiveness of drug removal is likely to be very limited if it is not begun immediately. In one case [37], when drug removal was begun 30 minutes after the incident, only 23% of the dose was recovered. In the case in which a more aggressive method of drug removal (ventriculolumbar "washout") was used [36], the attempt at recovery did not begin until 4.5 hours after the error, and that child, like the others, died.

Anthracycline intrathecal injection. CSF exchange, followed by continuous CSF drainage, did not appear to be effective in the case involving daunorubicin. That child experienced a progressive encephalopathy and eventually died. However, the pharmacokinetic characteristics of the anthracyclines provide a basis for suggesting an alternative technique. Since anthracyclines (similar to vinca alkaloids) undergo extensive tissue and plasma protein binding, CSF exchange plus ventriculolumbar perfusion—using a solution containing protein—might be effective [43,44,46].

Despite the fact that no attempt was made in the nonfatal case, drug removal should still be considered. The survivor suffered potentially life-threatening toxicities, and the literature is too sparse to conclude that the fatality was an anomaly.

Folinic Acid

Folinic acid was given systemically following an intrathecal overdoses of methotrexate, vinca alkaloid intra-

venous overdoses, and vincristine intrathecal injections. Since the use of folinic acid with methotrexate is a familiar practice, most of this discussion will be restricted to its use in incidents involving vinca alkaloids. Some comments, however, can be made about cases involving a massive methotrexate intrathecal overdose. Folinic acid appeared to provide no protection against insult to the CNS. Although Spiegel et al. [41] did add folinic acid to a portion of the fluid during ventriculolumbar perfusion, there was no evidence that this resulted in any significant benefit.

Vinca alkaloid intravenous overdose. The evidence for any benefit from folinic acid is scanty. Although in some instances toxicities were reported to have been of shorter duration, drug removal is more likely to have been responsible for these observations in two of the cases [20].

The mechanism for folinic acid's putative beneficial effects is, at this time, entirely speculative. It has been postulated that it works by overcoming a vinca alkaloid–mediated block of dihydrofolate reductase, or by the restoring cellular capacity to synthesize RNA and proteins [20,29]. Furthermore, there has not been any controlled trial demonstrating its effectiveness in reducing toxicities associated with vinca alkaloids.

If folinic acid is used, the suggested dosage is 7 mg/kg/day, given IV. This dosage is based on a best outcome case described by Kosmidis et al. [20]. However, it should be pointed out that 72% of the dose was recovered by double-volume exchange transfusion.

Vinca alkaloid intrathecal injection. There is little evidence that folinic acid is effective for ameliorating the devastating insult to the CNS caused by vincristine. Furthermore, children who received folinic acid still developed characteristic vinca alkaloid-induced toxicities: loss of deep tendon reflexes, urinary retention, and paralytic ileus.

Nevertheless, consideration might still be given to using folinic acid. The seriousness of the intrathecal injection of a vinca alkaloid is such that aggressive treatment should be pursued, and the child reported on by Gaidys et al. [36] did experience a transient recovery of reflexes. The suggested intervention is adapted from that case: folinic acid 8 mg/kg IV push stat, followed by 2 mg/kg/h as a continuous infusion. The duration of therapy must be *speculative*, but based on the estimated half-life of intrathecally injected vincristine (5 days) [32], 14 days may be appropriate.

Dexamethasone

Dexamethasone (or another corticosteroid) has been used following methotrexate intrathecal overdoses, intrathecal injections of vincristine, and intrathecal injections of an anthracycline.

Methotrexate intrathecal overdose. Based on outcome, corticosteroids did not appear to be effective in the cases involving overdoses of 650 mg or more, although dexamethasone may not have been started immediately in one fatal case [2]. The etiology of the damage to the CNS is unknown, but it would be reasonable to expect meningeal inflammation. While evidence of CNS demyelination was reported in one fatal case [2], it is not certain that CNS neurotoxicity is due to a direct chemical effect. Cell death has not been observed in the case of neurons exposed in vitro to methotrexate [47].

Vinca alkaloid intrathecal injection. Meningeal inflammation should be anticipated. Immediate administration of dexamethasone may be of benefit, but the duration of therapy affording a better outcome must be speculative.

Anthracycline intrathecal injection. Increased intracranial pressure and meningeal inflammation should be anticipated, and it would be prudent to consider starting dexamethasone immediately. There is little information to provide a basis for suggesting the most effective duration of therapy. The child who received doxorubicin was given dexamethasone shortly after the incident, but still developed hydrocephalus 2 weeks later.

Intrathecal Corticosteroids

There is no evidence that an intrathecal corticosteroid has any role in management. Hydrocortisone was given by this route following the intrathecal injection of both vincristine and daunorubicin [18,31,37], and all of these cases were fatalities.

It is not possible to discriminate between damage due to an antineoplastic agent and any possible harm from using an intrathecal steroid in deciding if the latter may actually increase the risk of a fatal outcome. It is known that of all reported pediatric cases of patients receiving a dose intrathecally that should not have been given by that route, only one survived, and that child did not receive an intrathecal steroid [17]. Moreover, the survivor of the intrathecal injection of vincristine [45] did not receive a steroid at all, nor did the patient reported on by Spiegel et al. [41] in the case of a massive intrathecal overdose of methotrexate.

PREVENTION

Several suggestions can be made about the prevention of errors. Work should be double-checked at each step. Measured height and weight should also be checked against standard graphs of age-appropriate percentiles. Preprinted forms, or a computer spreadsheet program, are two means of verifying that dosage and body *surface* area (BSA) calculations are correct, and orders should be explicitly written in terms of body mass or BSA. An oncology pharmacist, for example, could make the initial

calculations, and the responsible oncologist could review them before signing the order.

The dispensing pharmacist should recheck the calculations, and a second pharmacist should compare what has been prepared by a technician with the original order. The protocol under which the order has been written should also be available in the dispensary. A dose that must not be given intrathecally should be labelled as such, and should be physically separated from those that are intended for systemic administration. One method of doing this is to dispense doses in separate plastic bags, each labelled with the appropriate route.

A necessary component in these steps is that they be carried out by persons who are trained in anticancer chemotherapy. Drugs should be ordered, prepared, and administered by persons who know what drug can be given by what route, in what amount, and at what interval.

Rescue therapy for the misadministration of an antineoplastic agent may require aggressive measures that themselves put a patient at risk for complications. The best treatment is prevention, and prevention of medication errors with potentially tragic consequences depends on consistency, accuracy, and expertise.

CONCLUSIONS

The interventions suggested here have been made on the basis of the case literature, which is meager and which describes experiences that were not the result of controlled trials. The authors advise that clinicians consider what is the most rational therapy for a particular patient and adapt these interventions accordingly. If an error occurs, it should be considered a medical emergency until a review of past experiences and a clinical assessment of the patient provide evidence to the contrary.

The most effective means of managing errors is prevention. Ordering, preparation, and administration of antineoplastic agents should be done by personnel who have been trained in anticancer chemotherapy and who are *familiar with* standard dosages and routes of administration. Furthermore, dosages and routes should be counterchecked. In the case of dosages, particular attention should be paid to the possibility of a decimal error or a change in the concentration of a stock solution.

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